08/656,811 search 1

?b 154,155,72,73,5,55,350,351,652,653,654

13/3,AB/1 (Item 1 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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13103969 BIOSIS Number: 99103969
Characterization and phosphorylation of CREB-like proteins in Aplysia central nervous system
Dash P K; Moore A N
Dep. Neurobiol. Anatomy, Univ. Texas- Houston Health Sci. Cent., PO Box 20708, Houston, TX 77225, USA
Molecular Brain Research 39 (1-2). 1996. 43-51.
Full Journal Title: Molecular Brain Research
ISSN: 0169-328X
Language: ENGLISH
Print Number: Biological Abstracts Vol. 102 Iss. 005 Ref. 069418
Studies in Aplysia californica indicate that cAMP-mediated gene expression is necessary for long-term facilitation, a correlate of long-term memory. It has been shown that blocking the expression of cAMP-inducible genes in sensory neurons impedes long-term facilitation without any effect on short-term facilitation. Specifically, blocking the binding of CREB-like proteins or inhibiting the expression of a cAMP-inducible gene, *CREBP*, impairs long-term facilitation. In this report, we show the presence of a family of CREB-like proteins in Aplysia CNS that specifically bind to the CRE sequence and cross-react with rat CREB antibodies. Similar to mammalian CREB proteins, Aplysia homologues
interact with each other via leucine zipper domains. This interaction can be disrupted by peptides containing the CREB leucine zipper sequence. We demonstrate that a 43 kDa CREB-like protein present in CNS extracts can be phosphorylated in vitro by cAMP-dependent protein kinase A. Moreover, exposure of ganglia to serotonin (5-HT), a transmitter involved in long-term facilitation, increases the phosphorylation of this protein. This biochemical data further supports the involvement of *CREB*-like proteins in *memory* storage.

13/3,AB/2 (Item 1 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)
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13103969 BIOSIS Number: 99103969
Characterization and phosphorylation of CREB-like proteins in Aplysia central nervous system
Dash P K; Moore A N
Dep. Neurobiol. Anatomy, Univ. Texas- Houston Health Sci. Cent., PO Box 20708, Houston, TX 77225, USA
Molecular Brain Research 39 (1-2). 1996. 43-51.
Full Journal Title: Molecular Brain Research
ISSN: 0169-328X
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Studies in Aplysia californica indicate that cAMP-mediated gene expression is necessary for long-term facilitation, a correlate of long-term memory. It has been shown that blocking the expression of cAMP-inducible genes in sensory neurons impedes long-term facilitation without any effect on short-term facilitation. Specifically, blocking the binding of CREB-like proteins or inhibiting the expression of a cAMP-inducible gene, *CREBP*, impairs long-term facilitation. In this report, we show the presence of a family of CREB-like proteins in Aplysia CNS that specifically bind to the CRE sequence and cross-react with rat CREB antibodies. Similar to mammalian CREB proteins, Aplysia homologues
interact with each other via leucine zipper domains. This interaction can be disrupted by peptides containing the CREB leucine zipper sequence. We demonstrate that a 43 kDa CREB-like protein present in CNS extracts can be phosphorylated in vitro by cAMP-dependent protein kinase A. Moreover, exposure of ganglia to serotonin (5-HT), a transmitter involved in long-term facilitation, increases the phosphorylation of this protein. This biochemical data further supports the involvement of *CREB*-like proteins in *memory* storage.
?

16/3,AB/1 (Item 1 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 1997 Knight-Ridder Info. All rts. reserv.

08736297 94345380
Requirement of a critical period of transcription for induction of a late phase of LTP.
Nguyen PV; Abel T; *Kandel ER*
Howard Hughes Medical Institute, New York, NY.
Science (UNITED STATES) Aug 19 1994, 265 (5175) p1104-7, ISSN
0036-8075 Journal Code: UJ7
Contract/Grant No.: GM32099, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Repeated high-frequency trains of stimuli induce long-term potentiation (LTP) in the CA1 region that persists for up to 8 hours in hippocampal slices and for days in intact animals. This long time course has made LTP an attractive model for certain forms of long-term *memory* in the mammalian brain. A hallmark of long-term *memory* in the intact animal is a requirement for transcription, and thus whether the late phase of LTP (L-LTP) requires transcription was investigated here. With the use of different inhibitors, it was found in rat hippocampal slices that the induction of L-LTP [produced either by tetanic stimulation or by application of the cyclic adenosine monophosphate (*cAMP*) analog Sp-cAMPS
(Sp-cyclic adenosine 3',5'-monophosphorothioate)] was selectively prevented when transcription was blocked immediately after tetanization or during application of *cAMP*. As with behavioral *memory*, this requirement for transcription had a critical time window. Thus, the late phase of LTP in the CA1 region requires transcription during a critical period, perhaps because *cAMP*-inducible genes must be expressed during this period.

16/3,AB/2 (Item 2 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
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08327322 95351648
A molecular switch for the consolidation of long-term *memory*: *cAMP* -inducible gene expression.
Alberini CM; *Ghirardi M*; Huang YY; Nguyen PV; *Kandel ER*
Center for Neurobiology and Behavior, College of Physicians & Surgeons of Columbia University, New York, New York, USA.
Ann N Y Acad Sci (UNITED STATES) Jun 30 1995, 758 p261-86, ISSN
0077-8923 Journal Code: 5NM
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

16/3,AB/3 (Item 3 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 1997 Knight-Ridder Info. All rts. reserv.

08033690 95007783
cAMP contributes to mossy fiber LTP by initiating both a covalently mediated early phase and macromolecular synthesis-dependent late phase.
Huang YY; Li XC; *Kandel ER*
Howard Hughes Medical Institute Center for Neurobiology and Behavior, College of Physicians and Surgeons, Columbia University, New York, New York
10032.
Cell (UNITED STATES) Oct 7 1994, 79 (1) p69-79, ISSN 0092-8674 Journal Code: CQ4
Contract/Grant No.: GM32099, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Memory storage has a short-term phase that depends on preexisting proteins and a long-term phase that requires new protein and RNA synthesis. Hippocampal long-term potentiation (LTP) is thought to contribute to *memory* storage. Consistent with this idea, a cellular representation of these phases has been demonstrated in NMDA receptor-dependent LTP. By contrast, little is known about the NMDA receptor-independent LTP of the mossy fiber pathway. We find that mossy fiber LTP also has phases. Only late phase is blocked by protein and RNA synthesis inhibitors, but both phases are blocked by inhibitors of *cAMP*-dependent protein kinase, and both are stimulated by forskolin and Sp-cAMPS. During early phase, paired-pulse facilitation is occluded. This occlusion decays with the onset of late phase, consistent with its using a different mechanism. Thus, although Schaffer collateral and mossy fiber pathways use very different mechanisms for early phase, both use a *cAMP*-mediated mechanism for late phase.

16/3,AB/4 (Item 4 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

07883499 94185169
C/EBP is an immediate-early gene required for the consolidation of long-term facilitation in Aplysia.
Alberini CM; *Ghirardi M*; Metz R; *Kandel ER*
Howard Hughes Medical Institute, College of Physicians and Surgeons, Columbia University, New York, New York 10032.
Cell (UNITED STATES) Mar 25 1994, 76 (6) p1099-114, ISSN 0092-8674
Journal Code: CQ4
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The consolidation of long-term *memory* requires protein and mRNA synthesis. A similar requirement has been demonstrated for learning-related synaptic plasticity in the gill-withdrawal reflex of Aplysia. The monosynaptic component of this reflex can be reconstituted in vitro, where it undergoes both short- and long-term increases in synaptic strength in response to serotonin (5-HT), a neurotransmitter released during behavioral sensitization, a simple form of learning. As with sensitization, the long-term synaptic modification is characterized by a brief consolidation period during which gene expression is required. We find that during this phase, the transcription factor Aplysia CCAAT enhancer-binding protein (ApC/EBP) is induced rapidly by 5-HT and by *cAMP*, even in the presence of
protein synthesis inhibitors. Blocking the function of ApC/EBP blocks long-term facilitation selectively without affecting the short-term process. These data indicate that *cAMP*-inducible immediate-early genes have an essential role in the consolidation of stable long-term synaptic plasticity in Aplysia.

16/3,AB/5 (Item 5 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

07841968 93276294
Effects of *cAMP* simulate a late stage of LTP in hippocampal CA1 neurons.
Frey U; Huang YY; *Kandel ER*
Center for Neurobiology and Behavior, Howard Hughes Medical Institute, College of Physicians and Surgeons, Columbia University, New York, NY 10032.
Science (UNITED STATES) Jun 11 1993, 260 (5114) p1661-4, ISSN 0036-8075 Journal Code: UJ7
Contract/Grant No.: GM32099, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Hippocampal long-term potentiation (LTP) is thought to serve as an elementary mechanism for the establishment of certain forms of explicit *memory* in the mammalian brain. As is the case with behavioral *memory*, LTP in the CA1 region has stages: a short-term early potentiation lasting 1 to 3 hours, which is independent of protein synthesis, precedes a later, longer lasting stage (L-LTP), which requires protein synthesis. Inhibitors of cyclic adenosine monophosphate (*cAMP*)-dependent protein kinase (PKA)
blocked L-LTP, and analogs of *cAMP* induced a potentiation that blocked naturally induced L-LTP. The action of the *cAMP* analog was blocked by inhibitors of protein synthesis. Thus, activation of PKA may be a component of the mechanism that generates L-LTP.

16/3,AB/6 (Item 6 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

07638772 93213500
Activation of *cAMP*-responsive genes by stimuli that produce long-term facilitation in Aplysia sensory neurons.
Kaang BK; *Kandel ER*; Grant SG
Howard Hughes Medical Institute, Center for Neurobiology and Behavior, College of Physicians and Surgeons of Columbia University, New York, New York 10032.
Neuron (UNITED STATES) Mar 1993, 10 (3) p427-35, ISSN 0896-6273
Journal Code: AN8
Languages: ENGLISH
Document type: JOURNAL ARTICLE
One of the hallmarks of long-term *memory* in both vertebrates and invertebrates is the requirement for new protein synthesis. In sensitization of the gill-withdrawal reflex in Aplysia, this requirement can be studied on the cellular level. Here, long-term but not short-term facilitation of the monosynaptic connections between the sensory and motor neurons requires new protein synthesis and is reflected in an altered level of expression of specific proteins regulated through the *cAMP* second-messenger pathway. Using gene transfer into individual sensory neurons of Aplysia, we find that serotonin (5-HT) induces transcriptional activation of a lacZ reporter gene driven by the *cAMP* response element (CRE) and that this induction requires CRE-binding proteins (CREBs). The induction by 5-HT does not occur following a single pulse, but becomes progressively more effective following two or more pulses. Moreover, expression of GAL4-CREB fusion genes shows that 5-HT induction requires phosphorylation of CREB on Ser119 by protein kinase A. These data provide direct evidence for CREB-modulated transcriptional activation with long-term facilitation.

16/3,AB/7 (Item 7 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

06632643 90294902
Injection of the *cAMP*-responsive element into the nucleus of Aplysia sensory neurons blocks long-term facilitation.
Dash PK; Hochner B; *Kandel ER*
Howard Hughes Medical Institute, New York, New York.
Nature (ENGLAND) Jun 21 1990, 345 (6277) p718-21, ISSN 0028-0836
Journal Code: NSC
Languages: ENGLISH
Document type: JOURNAL ARTICLE
In both vertebrates and invertebrates, long-term *memory* differs from short-term in requiring protein synthesis during training. Studies of the gill and siphon withdrawal reflex in Aplysia indicate that similar requirements can be demonstrated at the level of sensory and motor neurons which may participate in *memory* storage. A single application of serotonin, a transmitter that mediates sensitization, to individual sensory and motor cells in dissociated cell cultures leads to enhanced transmitter release from the sensory neurons that is independent of new macromolecular synthesis. Five applications of serotonin cause a long-term enhancement, lasting one or more days, which requires translation and transcription. Prolonged application or intracellular injection into the sensory neuron of cyclic AMP, a second messenger for the action of serotonin, also produce long-term increases in synaptic strength, suggesting that some of the gene products important for long-term facilitation are *cAMP*-inducible. In eukaryotic cells, most *cAMP*-inducible genes so far studied are activated by the *cAMP* -dependent protein kinase (A kinase), which phosphorylates transcription factors that bind the *cAMP*-responsive element TGACGTCA. The
cAMP-responsive element (CRE) binds a protein dimer of relative molecular
mass 43,000, the CRE-binding protein (CREBP), which has been purified and shown to increase transcription when phosphorylated by the A kinase. Here we show that extracts of the Aplysia central nervous system and extracts of sensory neurons contain a set of proteins, including one with properties similar to mammalian CREBPs, that specifically bind the mammalian CRE sequence. Microinjection of the CRE sequence into the nucleus of a sensory neuron selectively blocks the serotonin-induced long-term increase in synaptic strength, without affecting short-term facilitation. Taken together, these observations suggest that one or more CREB-like transcriptional activators are required for long-term facilitation.

16/3,AB/8 (Item 8 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

06332684 89238542
Persistent and transcriptionally-dependent increase in protein phosphorylation in long-term facilitation of Aplysia sensory neurons.
Sweatt JD; *Kandel ER*
Howard Hughes Medical Institute, College of Physicians and Surgeons of Columbia University, New York 10032.
Nature (ENGLAND) May 4 1989, 339 (6219) p51-4, ISSN 0028-0836
Journal Code: NSC
Languages: ENGLISH
Document type: JOURNAL ARTICLE

From certain perspectives, short- and long-term *memory* seem to be a single behavioural process whose duration is a graded function of the number of training trials. Yet some clinical conditions can dissociate short- from long-term *memory* in human beings, and inhibitors of protein or RNA synthesis can selectively block the long-term process in experimental animals. Studies of *memory* for sensitization in the gill- and siphon-withdrawal reflex in Aplysia indicate that both the behavioural similarities and the differences are reflected in intrinsic cellular mechanisms in the sensory and motor neurons participating in *memory* storage. Although the long-term change in the synaptic connection between the sensory and motor neurons resembles a graded extension of the short-term change, its induction is selectively blocked by inhibitors of transcription or translation. We have now examined the molecular mechanisms in the sensory neurons that might account for the graded similarity between short- and long-term *memory*, as well as those that might contribute to the differential sensitivity to inhibitors of macromolecular synthesis. We find that a single exposure to 5-HT (a transmitter released in response to behavioural sensitizing stimuli) or cyclic AMP (a second messenger for 5-HT), which produce short-term facilitation between the sensory and motor neurons lasting minutes, leads to a short-term phosphorylation of 17 substrate proteins that is not dependent on transcription or translation. Repeated or prolonged exposure to serotonin or *cAMP* , which induce long-term changes in synaptic transmission lasting one or more days, induce long-term changes in phosphorylation of the same 17 proteins that are now dependent for their induction on both translation and transcription. Thus, one of the functions of the genes and proteins required for long-term facilitation may be to maintain actively in the sensory neurons an increased phosphorylation of the same set of substrate proteins involved in eliciting the physiological effects of the short-term process.

16/3,AB/9 (Item 1 from file: 72)
DIALOG(R)File 72:EMBASE

7753920 EMBASE No: 90182902
Protein synthesis during acquisition of long-term facilitation is needed for the persistent loss of regulatory subunits of the Aplysia *cAMP* -dependent protein kinase
Bergold P.J.; Sweatt J.D.; Winicov I.; Weiss K.R.; *Kandel E.R.*; Schwartz J.H.
Howard Hughes Medical Institute, Columbia University, College of Physicians and Surgeons, New York, NY 10032 USA
PROC. NATL ACAD. SCI. U. S. A. (USA), 1990, 87/10 (3788-3791) CODEN:
PNASA ISSN: 0027-8424
LANGUAGES: English
Depending on the number or the length of exposure, application of serotonin can produce either short-term or long-term presynaptic facilitation of Aplysia sensory-to-motor synapses. The *cAMP*-dependent protein kinase, a heterodimer of two regulatory and two catalytic subunits, has been shown to become stably activated only during long-term facilitation. Both acquisition of long-term facilitation and persistent activation of the kinase is blocked by anisomycin, an effective, reversible, and specific inhibitor of protein synthesis in Aplysia. We report here that 2-hr exposure of pleural sensory cells to serotonin lowers the concentration of regulatory subunits but does not change the concentration of catalytic subunits, as assayed 24 hr later; 5-min exposure to serotonin has no effect on either type of subunit. Increasing intracellular *cAMP* with a permeable analog of *cAMP* together with the phosphodiesterase inhibitor isobutyl methylxanthine also decreased regulatory subunits, suggesting that *cAMP* is the second messenger mediating serotonin action. Anisomycin blocked the loss of regulatory subunits only when applied with serotonin; application after the 2-hr treatment with serotonin had no effect. In the Aplysia accessory radula contractor muscle, prolonged exposure to serotonin or to the peptide transmitter small cardioactive peptide B, both of which produce large increases in intracellular *cAMP*, does not decrease regulatory subunits. This mechanism of regulating the *cAMP*-dependent protein kinase therefore may be specific to the nervous system. We conclude that during long-term facilitation, new protein is synthesized in response to the facilitatory stimulus, which changes the ratio of subunits of the *cAMP*-dependent protein kinase. This alteration in ratio could persistently activate the kinase and produce the persistent phosphorylation seen in long-term facilitated sensory cells.

16/3,AB/10 (Item 1 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

7661091 BIOSIS Number: 90029091
PROTEIN SYNTHESIS DURING ACQUISITION OF LONG-TERM FACILITATION IS NEEDED
FOR THE PERSISTENT LOSS OF REGULATORY SUBUNITS OF THE APLYSIA CYCLIC AMP
DEPENDENT PROTEIN KINASE
BERGOLD P J; SWEATT J D; WINICOV I; WEISS K R; *KANDEL E R*; SCHWARTZ J H
HOWARD HUGHES MED. INST., CENTER NEUROBIOL. BEHAVIOR, 722 WEST 168TH ST.,
NEW YORK, NY 10032.
PROC NATL ACAD SCI U S A 87 (10). 1990. 3788-3791. CODEN: PNASA
Full Journal Title: Proceedings of the National Academy of Sciences of the United States of America
Language: ENGLISH
Depending on the number or the length of exposure, application of serotonin can produce either short-term or long-term presynaptic facilitation of Aplysia sensory-to-motor synapses. The *cAMP*-dependent protein kinase, a heterodimer of two regulatory and two catalytic subunits, has been shown to become stably activated only during long-term facilitation. Both acquisition of long-term facilitation and persistent activation of the kinase is blocked by anisomycin, an effective, reversible, and specific inhibitor of protein synthesis in Aplysia. We report here that 2-hr exposure of pleural sensory cells to serotonin lowers the concentration of regulatory subunits but does not change the concentration of catalytic subunits, as assayed 24 hr later; 5-min exposure to serotonin has no effect on either type of subunit. Increasing intracellular *cAMP* with a permeable analog of *cAMP* together with the phosphodiesterase inhibitor isobutyl methylxanthine also decreased regulatory subunits, suggesting that *cAMP* is the second messenger mediating serotonin action. Anisomycin blocked the loss of regulatory subunits only when applied with serotonin; application after the 2-hr treatment with serotonin had no effect. In the Aplysia accessory radula contractor muscle, prolonged exposure to serotonin or to the peptide transmitter small cardioactive peptide B, both of which produce large increases in intracellular *cAMP*, does not decrease regulatory subunits. This mechanism of regulating the *cAMP*-dependent protein kinase therefore may be specific to the nervous system. We conclude that during long-term facilitation, new protein is syntehsized in response to the facilitatory stimulus, which changes the ratio of subunits of the *cAMP*-dependent protein kinase. This alteration in ratio could persistently activate the kinase and produce the persistent phosphorylation seen in long-term facilitated sensory cells.
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24/3,AB/1 (Item 1 from file: 72)
DIALOG(R)File 72:EMBASE

8095382 EMBASE No: 91126863
A role for protein kinase C in associative learning
Olds J.L.; Alkon D.L.
Laboratory of Molecular and Cellular Neurobiology, National Institutes of Health, Bldg 9, Bethesda, MD 20892 USA
NEW BIOL. (USA), 1991, 3/1 (27-35) CODEN: NEBIE ISSN: 1043-4674
LANGUAGES: English
Recent work suggests that protein kinase C (PKC), an enzyme that has a critical role in the regulation of cell growth and differentiation, also participates in the sequence of molecular events that underlie learning and memory. By means of electrophysiological, biochemical, and neuro-imaging methods it has been demonstrated that, in the brain, the distribution of PKC changes as a result of memory storage. The changes in distribution occur within the same ensembles of nerve cells that are necessary for the acquisition and performance of various learning tasks in several species. Here we review the data pertaining to a model that has been proposed to account for the participation of PKC as a molecular signal for cotemporal synaptic input during associative learning.

24/3,AB/2 (Item 2 from file: 72)
DIALOG(R)File 72:EMBASE

7931790 EMBASE No: 90360668
Neurotoxicity of excitatory amino acids
Duncan P.

Information Network, Fidia Pharmaceutical Corp., Washington, DC USA
DRUG NEWS PERSPECT. (Spain), 1990, 3/1 (59-62) CODEN: DNPEE
ISSN:
0214-0934
LANGUAGES: English

24/3,AB/3 (Item 3 from file: 72)
DIALOG(R)File 72:EMBASE
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6391324 EMBASE No: 87127984
Abnormal temporal lobe response in Alzheimer's disease during cognitive processing as measured by sup 1sup 1C-2-deoxy-D-glucose and PET
Miller J.D.; De Leon M.J.; Ferris S.H.; et al.
Department of Radiology, New York University Medical Center, New York, NY
10016 USA
J. CEREB. BLOOD FLOW METAB. (USA), 1987, 7/2 (248-251) CODEN: JCBMD
LANGUAGES: ENGLISH
Elderly controls and probable Alzheimer's disease patients underwent serial positron emission tomography (PET) studies during a baseline condition and while performing a verbal memory task. For the temporal lobes, all 7 Alzheimer patients demonstrated a relative shift in glucose metabolic rates to the right hemisphere during the memory condition relative to baseline, and 5 of 7 controls showed a shift to the left hemisphere. Baseline absolute regional metabolic rates replicate previous findings and were womewhat less useful than the memory challenge in differentiating patients from controls. These results indicate that a temporal lobe abnormality in Alzheimer's disease is related to memory performance.

24/3,AB/4 (Item 1 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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12040040 BIOSIS Number: 98640040
Hippocampal muscarinic receptor function in spatial learning-impaired aged rats
Chouinard M L; Gallagher M; Yasuda R P; Wolfe B B; McKinney M
Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA
Neurobiology of Aging 16 (6). 1995. 955-963.
Full Journal Title: Neurobiology of Aging
ISSN: 0197-4580
Language: ENGLISH
Print Number: Biological Abstracts Vol. 101 Iss. 004 Ref. 055785
Efficiency of coupling of hippocampal muscarinic receptors to phosphoinositide (PI) turnover was investigated in behaviorally characterized young and aged Long-Evans rats using hippocampal minces and the method of partial receptor alkylation of Furchgott. Densities of the m1, m2, and m3 receptor proteins were determined using specific antibodies and immunoprecipitation. Spatial learning ability was quantified using a water maze. There were no differences in the levels of muscarinic receptor proteins between young and aged (27 months) rats or in rats with impaired spatial learning. The dissociation constant (K-D) for the agonist oxotremorine-M and the K-D/EC-50 ratio, an indicator of receptor-effector coupling efficiency were similar in young and aged rats. However, the maximal PI turnover response to oxotremorine-M was decreased in impaired aged rats and this parameter was highly correlated with the spatial learning index (R = -0.825; p lt 0.001). A reduction in effector stimulation in the absence of changes in receptor protein or coupling efficiency suggests that dysfunction in the hippocampal muscarinic receptor systems occurs at the level of phospholipase C or beyond.

24/3,AB/5 (Item 2 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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10134238 BIOSIS Number: 95134238
MEMORY PROCESSING AND APAMIN INDUCE IMMEDIATE EARLY GENE EXPRESSION IN MOUSE BRAIN
HEURTEAUX C; MESSIER C; DESTRADE C; LAZDUNSKI M
INST. PHARMACOLOGIE MOLECULAIRE CELLULAR, 660 ROUTE DES LUCIOLES, SOPHIA ANTIPOLIS, 06560 VALBONNE, FR.
MOL BRAIN RES 18 (1-2). 1993. 17-22. CODEN: MBREE
Full Journal Title: Molecular Brain Research
Language: ENGLISH
The present study analyses the effects of learning on the spatial pattern and the time-course of changes of immediate early gene messenger RNA's (c-fos and c-jun) in mouse brain produced by training in an appetitive bar-pressing task. Activation of c-fos and c-jun after training is strictly located in the hippocampal formation and is learning-dependent. Levels of both proto-oncogene mRNAs in the trained group were 4 to 5 times higher than in the sham-conditioned group. Injections of apamin, a bee venom neurotoxin that selectively blocks a class of Ca2+-activated K+ channels and improves learning and memory retention, produced as compared to untrained animals a 3- to 5-fold increase of expression of c-fos and c-jun with the same pattern as that observed in the trained animals. Post-training injection of 0.2 mg/kg apamin enhanced 1.4-fold the expression of both immediate early genes in CA1, CA3 and dentate gyrus as compared to trained saline-injected mice. All these results suggest that apamin-induced increase of immediate early gene expression might be related to the apamin-induced facilitation of learning.

24/3,AB/6 (Item 3 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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7337779 BIOSIS Number: 38118300
ALZHEIMER BETA PEPTIDE PROTEIN KINASE *C* AND *MEMORY*
BROCKERHOFF H; CHAUHAN V P S; WISNIEWSKI H W; CHAUHAN A
N.Y.S. INST. BASIC RES. DEV. DISABILITIES, 1050 FOREST HILL ROAD, STATEN ISLAND, N.Y. 10314, USA.
74TH ANNUAL MEETING OF THE FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY, PART II, WASHINGTON, D.C., USA, APRIL 1-5, 1990.
FASEB (FED AM SOC EXP BIOL) J 4 (4). 1990. A699. CODEN: FAJOE
Language: ENGLISH
Document Type: CONFERENCE PAPER

24/3,AB/7 (Item 1 from file: 351)
DIALOG(R)File 351:DERWENT WPI
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007500596
WPI Acc No: 88-134529/198820
XRAM Acc No: C88-060095
1,3-Dibutyl-7-hydroxypropyl-xanthine - used for treating cerebral, vascular and skin disorders
Patent Assignee: BEECHAM GROUP PLC (BEEC); BEECHAM WUELFING GMBH & CO KG (BEEC)
Inventor: ANGERSBACH D; ARCH J R S; GORING J; MORGAN B; NICHOLSON C D
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Main IPC	Week
EP 267676	A	19880518	EP 87307977	A	19870909		198820 B
JP 63079832	A	19880409	JP 87227523	A	19870910		198820
US 4784999	A	19881115	US 8796118	A	19870911		198848

Priority Applications (No Type Date): GB 8621869 A 19860911
Filing Details:
Patent Kind Filing Notes Application Patent
EP 267676 A
Designated States (Regional): BE CH DE FR GB IT LI NL
Language, Pages: EP 267676 (E, 6); US 4784999 (4)
Abstract (Basic): EP 267676 A
1,3-Di-n-butyl-7-(2-hydroxypropyl) xanthine (I) or its salts are used for the mfr. of medicaments for treating (a) cerebrovascular and neuronal degenerative disorders associated with learning, *memory* and cognitive dysfunctions, including cerebral senility, multi-infarct dementia and *Alzheimer*'s disease, and/or (b) peripheral vascular disease and/or (*c*) proliferative skin disease. (I) is described in DE926788 (as a diuretic).
ADVANTAGE - (I) has a protective effect against the consequences of cerebral metabolic inhibition, improves data acquisition and retrieval following transient forebrain ischaemia, increases oxygen

tension in ischaemic skeletal muscle and acts as a phosphodiesterase inhibitor and increases cAMP levels. (I) is administered orally, parenterally or topically in unit doses of 0.1-500 (esp. 2-50) mg.. The daily dose is 0.002-5

Abstract (Equivalent): US 4784999 A

Treatment of cerebral vascular and neuronal degenerative disorders related to learning, memory and cognitive dysfunctions comprises admin. 1,3-di-n-butyl-7-(2-oxypropyl)-xanthine or salt. These disorders include cerebral senility, multi-infarct dementia, and Alzheimer demntia, and also peripheral vascular disease and proliferative skin desease.

USE - Treatment of above conditions at dosage e.g., 0.1-500 (2-50) mg/day. Action of inhibition of phosphodiesterase and increase in cAMP.

24/3,AB/8 (Item 1 from file: 654)
DIALOG(R)File 654:US PAT.FULL.

01935861

Utility

PHARMACEUTICAL FORMULATIONS FOR PARENTERAL USE

[Decreasing precipitation at injection site or in lungs or other organs by combining with hydroxypropyl-beta-cyclodextrin]

PATENT NO.: 4,983,586
ISSUED: January 08, 1991 (19910108)
INVENTOR(s): Bodor, Nicholas S., Gainesville, FL (Florida), US (United States of America)
ASSIGNEE(s): University of Florida, (A U.S. Company or Corporation), Gainesville, FL (Florida), US (United States of America)
[Assignee Code(s): 31139]
APPL. NO.: 7-174,945
FILED: March 29, 1988 (19880329)

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of applicant's copending application Ser. No. 139,755, filed Dec. 30, 1987 for "IMPROVEMENTS IN
REDOX SYSTEMS FOR BRAIN-TARGETED DRUG DELIVERY", incorporated by reference
herein in its entirety and relied upon.

FULL TEXT: 4285 lines

ABSTRACT

Aqueous parenteral solutions of drugs which are insoluble or only sparingly soluble in water and/or which are unstable in water, combined with hydroxypropyl- beta -cyclodextrin, provide a means for alleviating problems associated with drug precipitation at the injection site and/or in the lungs or other organs following parenteral administration.
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